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Does co-occurring anxiety modulate ADHD-related cognitive and neurophysiological impairments?

Journal:	<i>Journal of Attention Disorders</i>
Manuscript ID	JAD-19-03-101.R1
Manuscript Type:	Article
Keywords:	Attention-Deficit/Hyperactivity Disorder, Anxiety, Comorbidity, Event-related potentials, Cognitive Performance
Abstract:	<p>Objective: This study investigates whether anxiety modulates cognitive-performance, electrophysiological and electrodermal processes that we previously found impaired in individuals with ADHD.</p> <p>Method: Self-reported anxiety symptoms, cognitive-electrophysiological measures of response inhibition, working memory, attention, conflict-monitoring, error-processing, and peripheral arousal during three cognitive tasks were obtained from 87 adolescents and young adults with ADHD and 169 controls. We tested the association of anxiety symptoms with each measure and whether controlling for anxiety symptoms attenuates the ADHD-control difference for each measure.</p> <p>Results: Individuals with ADHD showed significantly elevated anxiety symptoms compared to controls. Only commission errors on a Continuous Performance Test (measuring response inhibition) were significantly associated with anxiety symptoms and only among controls, with the ADHD-control difference in this measure remaining significant.</p> <p>Conclusion: Using a wide range of cognitive, electrophysiological and electrodermal measures, our investigation suggests, overall, limited malleability of these impairments in individuals with ADHD irrespective of their levels of anxiety.</p>

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Effects of anxiety on ADHD-related impairments

INTRODUCTION

Anxiety is one of the most frequent psychiatric comorbidities in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) (Elia, Ambrosini, & Berrettini, 2008; Larson, Russ, Kahn, & Halfon, 2011). Individuals with ADHD who have a co-occurring anxiety disorder show greater functional impairment, as well as social and emotional problems, than those with ADHD alone (Bowen, Chavira, Bailey, Stein, & Stein, 2008), and the response to ADHD medications may be attenuated in the presence of co-occurring anxiety disorders or symptoms (Jensen et al., 2001; Moshe, Karni, & Tirosh, 2012). Poorer long-term outcomes have also been reported, in that youths with comorbid ADHD and anxiety have a higher risk of developing emotional and social problems later in life than those with ADHD only (Angold, Costello, & Erkanli, 1999; Halmoy, Fasmer, Gillberg, & Haavik, 2009; Newcorn et al., 2004; Tannock, 2009).

To understand the mechanisms underlying the poor functioning and outcomes in individuals with ADHD and comorbid anxiety, investigators have examined whether anxiety has an impact on the cognitive impairments typically associated with ADHD. Early theoretical models proposed that anxiety symptoms of worry have damaging effects on storing and processing capacities of verbal working memory, ultimately interfering with attentional control (Eysenck, Derakshan, Santos, & Calvo, 2007; Humphreys & Revelle, 1984). This was supported by the results of initial studies on individuals with ADHD (Schatz & Rostain, 2006; Tannock, 2009). A second existing hypothesis additionally proposes a ‘protective’ role of anxiety for inhibitory deficits (Schatz & Rostain, 2006). The interference account of anxiety on inhibitory control in ADHD has been tentatively explained with an improved balance between Quay’s behavioural inhibition system (BIS) and behavioural activation system (BAS) (Schatz & Rostain, 2006). By pooling the results of 11 studies, a recent meta-analysis suggested that, relative to individuals with ADHD alone (n=695), those with both ADHD and an anxiety disorder (n=608) had better response inhibition, but did not differ on attention or working memory measures (Maric, Bexkens, & Bogels, 2018). While supporting the potential attenuation effects of anxiety on inhibitory

Effects of anxiety on ADHD-related impairments

deficits in individuals with ADHD, this more recent evidence does not corroborate the negative interference of anxiety on attention and working memory functions in ADHD. Yet, it was noted that wide age ranges and predominantly male samples may limit the effects on attention and working memory, respectively (Maric et al., 2018).

A few other studies have investigated the effects of comorbid anxiety on cognitive processes in individuals with ADHD when measuring anxiety as a continuum rather than as a diagnosis. Findings have indicated that high anxiety ratings were associated with better inhibition in both youths with ADHD and controls (Bloemsma et al., 2013; Ruf, Bessette, Pearlson, & Stevens, 2017). Only one of these studies tested the association of anxiety with working memory performance, showing no significant effects of anxiety on this measure (Bloemsma et al., 2013). For attention and vigilance measures, the findings have been mixed. One study reported that high anxiety traits in individuals with ADHD were associated with reduced omission rates, mean response speed and response variability in a continuous performance task (Ruf et al., 2017), while another study using a simple reaction time (RT) task indicated slower response speed in relation to anxiety traits (Bloemsma et al., 2013). Of note, in a recent study the attenuation effects of anxiety on measures of attention (omissions), response speed and variability were observed in youths with ADHD, but not in controls (Ruf et al., 2017), suggesting malleability of these cognitive functions in relation to anxiety only in individuals with ADHD. Overall, dimensional and categorical approaches converge in supporting the putative protective role of anxiety on inhibitory deficits in ADHD, but findings are mixed on whether attention and memory impairments in individuals with ADHD are affected by anxiety. Further, previous studies suggest that while co-occurring anxiety symptoms reduced the level of impairments observed in individuals with ADHD on a number of cognitive measures, the ADHD-control differences remained significant (Ruf et al., 2017). Therefore it remains unclear whether anxiety effects produce meaningful attenuations on the observed ADHD-related impairments.

Effects of anxiety on ADHD-related impairments

Investigations on the moderating effects of anxiety in individuals with ADHD have almost entirely focused on cognitive performance. Although atypical profiles have also been documented at the brain level in ADHD in several electroencephalography (EEG) studies (Johnstone, Barry, & Clarke, 2013; Tye, McLoughlin, Kuntsi, & Asherson, 2011), little is known about the mechanisms of the potential protective or interfering roles of anxiety on these impairments. Using event-related potentials (ERPs), one small-scale study examined the similarities and differences on neurophysiological impairments between participants with ADHD only and those with comorbid ADHD and an anxiety disorder (Klymkiw et al., 2017). Youth with both ADHD and an anxiety disorder showed milder impairments in response inhibition (commission errors) and ERP activity of conflict-monitoring (N2 following no-go stimuli), as well as in early EEG measures reflecting auditory selective attention (early frontal positivity during a selective auditory attention task), compared to those with ADHD only (Klymkiw et al., 2017). Thus, by measuring the brain dysfunctions in ADHD with and without co-occurring anxiety symptoms, the use of EEG measures may shed light on which cognitive and brain processes are linked to the modulating effects of anxiety in ADHD.

Another physiological measure that may help understand the role of anxiety on the ADHD-related impairments is skin conductance (SC), a measure of electrodermal activity and an objective index of arousal in the peripheral nervous system (Boucsein, 1992). Elevated SC tonic levels and reactivity to threat stimuli are well-known associated features of anxiety (Craske et al., 2008; Erath, Tu, & El-Sheikh, 2012). Our group previously demonstrated that individuals with ADHD show lower tonic levels of peripheral arousal measured with SC during a simple 4-choice RT task, relative to controls (James, Cheung, et al., 2017). Yet, no study to date has investigated whether anxiety moderates arousal impairments in individuals with ADHD.

In the present study, we investigate whether anxiety modulates the cognitive, physiological and brain impairments that have been shown to link to ADHD in our previous analyses on adolescents and young

Effects of anxiety on ADHD-related impairments

adults with ADHD and typically developing controls (Cheung et al., 2017; Cheung et al., 2016; James, Cheung, et al., 2017; Michelini et al., 2018; Michelini et al., 2016). In a preliminary step, we aim to confirm previous findings that individuals with ADHD have elevated anxiety symptoms relative to controls (Elia et al., 2008). We then test whether high anxiety levels associate with a range of cognitive-performance, EEG and skin conductance measures of response inhibition, working and short-term memory, attention, error processing and peripheral arousal, both in individuals with ADHD and, for comparison, in controls. While it could be hypothesised that high anxiety traits are related to better response-inhibition measures, no formal predictions were made for the attenuation or exacerbation effects of anxiety on attention, memory and neurophysiological measures owing to the limited and inconsistent existing literature. If a significant interaction effect between anxiety symptoms and group emerges, we further examine whether the ADHD-control difference on the measure is significantly attenuated when controlling for anxiety symptoms. Finally, given previous findings of attenuated cognitive impairments in presence of anxiety in samples with higher proportion of males than females (Maric et al., 2018), and given that our sample includes only a small number of females, we repeat the analyses when including male participants only.

METHODS

Sample

ADHD and control groups, who had taken part in previous research (W. Chen et al., 2008; Kuntsi et al., 2010), were invited to take part in a follow-up study (Cheung et al., 2016; Cheung et al., 2015; Michelini et al., 2018). The ADHD group was initially recruited from specialised ADHD clinics in the UK, and the control group was recruited from primary and secondary schools in the UK. Exclusion criteria for both groups included IQ<70, autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalising behaviours that might mimic ADHD. After exclusion of the participants with childhood-ADHD that no longer met criteria for ADHD (n=25) and controls meeting ADHD criteria

Effects of anxiety on ADHD-related impairments

(n=9) at follow-up, the final sample consisted of 87 individuals with an ADHD diagnosis at follow-up (14 full pairs, 73 singletons) and 169 control siblings (76 full pairs, 17 singletons) (Table 1). Written informed consent was obtained following procedures approved by the London-Surrey Borders Research Ethics Committee (09/H0806/58).

Procedure

Participants attended a single 4.5h research session, which included a cognitive-EEG assessment, an IQ test and clinical interviews, including the Diagnostic Interview for ADHD in adults (DIVA) (Kooij & Francken, 2007) and the Barkley Functional Impairment Scale (BFIS) (Barkley & Murphy, 2006). Parent-reported ADHD symptoms and impairment obtained from face-to-face clinical interviews were used to determine ADHD status in the ADHD group and parent-reported ADHD ratings were used to identify controls meeting ADHD diagnostic criteria, as described previously (Cheung et al., 2016; James, Cheung, Rijdsdijk, Asherson, & Kuntsi, 2016; Michelini et al., 2016). For the participants with ADHD who were being treated with stimulant medications (n = 43), a 48-hr ADHD medication-free period was required prior to the cognitive-EEG assessments. Information on lifetime use of non-pharmacological interventions for ADHD or history of treatment for anxiety disorders was not available.

Measures

Anxiety symptoms

The Clinical Interview Schedule Revised (CIS-R) was used to identify symptoms of anxiety. The anxiety disorders sections of this semi-structured interview were conducted by trained researchers with the participants as part of a research diagnostic assessment. Each of the Anxiety, Phobias and Panic disorders scales included items relating to the severity and duration of symptoms (Lewis, Pelosi, Araya, & Dunn, 1992). The anxiety symptoms scores were formed by combining the sum of yes/no (i.e., 1 or 0) scores from four subscales: a subscale of 'worry', a subscale of 'anxiety', a subscale of 'phobias' and a subscale 'panic', each with a maximum score of 4. As a result, the total anxiety symptoms score was

Effects of anxiety on ADHD-related impairments

comprised of 36 items, with a maximum score of 16. Obsessive-compulsive traits were also examined as part of the interview and included in the anxiety symptoms scores in a supplementary analysis; obsessive-compulsive traits included the obsessions and compulsions subscales, each giving a maximum score of 4. The CIS-R has good internal validity with a Cronbach's alpha score of 0.82 reported (Lewis et al., 1992), and was developed for use by non-clinical interviewers.

IQ and memory estimates

The verbal and performance design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) were administered to all participants to derive IQ estimates. The digit span subtest from the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991) or the WAIS-III (Wechsler, 1997) was administered to participants aged below 16 and 16 or above, respectively, to obtain digit span forward and backward. The forward test measures short-term verbal memory, while the backward test is a measure of working memory.

The Cued-Continuous Performance Test (CPT-OX)

The CPT-OX is a cued Go/NoGo task that probes attention, preparation and response inhibition (Doehnert, Brandeis, Imhof, Drechsler, & Steinhausen, 2010). The task consists of 400 black letter arrays, formed of a centre letter and incompatible flankers on each side. The task involves the pseudorandomized presentation of 80 Cues ("XOX") followed either by 40 Go ("OXO") and 40 NoGo ("XDX") stimuli, or by random letter arrays as neutral distractors (e.g. "XBX"). Participants were instructed to respond only to target letters in Cue-Go sequences, and to withhold the response in presence of a NoGo stimulus, or a Go not preceded by a Cue (40 trials), or of any other irrelevant letters. Task duration was approximately 11 min.

The Arrow Flanker task

The task was an adaptation of the Eriksen flanker paradigm designed to increase cognitive load as

Effects of anxiety on ADHD-related impairments

used in previous studies (Albrecht et al., 2008; McLoughlin et al., 2009). In each trial a central black fixation mark was replaced by a target arrow (a black 18-mm equilateral triangle). Participants had to indicate whether this arrow pointed towards the left or right by pressing corresponding buttons with their left or right index fingers. Both flankers either pointed in the same (congruent) or opposite (incongruent) direction to the target. As such, conflict monitoring is maximal during the incongruent condition.

The Fast Task

Participants performed a four-choice RT task with a baseline condition (72 trials) with four empty circles (warning signals, arranged horizontally) first appearing for 8000ms, after which one of them (the target) was coloured in (Kuntsi, Andreou, Ma, Borger, & van der Meere, 2005). Participants were asked to press the response key that directly corresponded to the position of the target. A comparison condition with a fast event rate (1000ms) and incentives followed the baseline condition (Kuntsi et al., 2005).

EEG recording and ERP analysis

The signals were recorded from a 62-channels DC-coupled recording system (extended 10–20 montage) and 2 electro-oculogram electrodes (Brain Products, Germany). Standard down-sampling of the data to 256 Hz, digital band-pass filtering (0.1–30 Hz, 24 dB/oct), re-referencing to the average reference and eye movement correction are described in (Cheung et al., 2017; Cheung et al., 2016; Michelini et al., 2016). ERPs were extracted from the CPT-OX (CNV, Go-P3, NoGo-P3), arrow Flanker task (N2, Pe, ERN, incongruent condition only) and Fast Task (CNV and P3) following procedures used on previous analyses of this sample ((Cheung et al., 2017; Cheung et al., 2016; Michelini et al., 2016); see Supplementary Material 1 for further detail).

Skin conductance (SC)

Effects of anxiety on ADHD-related impairments

SC data were recorded with reusable 8mm diameter silver-silver chloride electrodes on the participant's non-dominant hand using PSYCHLAB SC5 24-bit equipment system (PSYCHLAB, UK). SC data were extracted from the Fast Task involving a skin conductance system based on a SC sigmoid-exponential model (Boucsein, 1992; Figner & Murphy, 2011; Lim et al., 1997; L. M. Williams et al., 2000), as described previously (James et al., 2016) (see Supplementary Material 1 for further detail). The tonic measure of SC levels was disentangled from phasic stimulus-associated SC responses and both measures were calculated per participant in each condition.

Statistical analyses

Comparison on anxiety symptoms between participants with ADHD and control individuals

The association between ADHD and anxiety symptoms was examined using a regression analysis that included anxiety symptoms as the dependent variable and a binary ADHD status variable (ADHD and control) as a main effect. The anxiety symptoms scores, measured as the number of total anxiety symptoms, were modeled as ordinal. To correct for the non-independence of the data of siblings in the ADHD and control groups, the correlation structure of the data was accounted for by calculating robust standard errors using the cluster command in Stata 14 (StataCorp) (R. L. Williams, 2000). The age range was wide in our sample, thus age was included as a covariate in the analysis. Effect sizes (Cohen's d), which were calculated using the difference in the means divided by the pooled standard deviation, are reported.

Variable selection

The starting point for selecting variables for analysis was to focus on cognitive and neurophysiological measures which previously showed ADHD-control differences in this sample (Cheung et al., 2017; Cheung et al., 2016; James, Rommel, et al., 2017; Michelini et al., 2016). To reduce the number of statistical comparisons, in this analysis we only include those variables where the previously reported ADHD-control differences were of moderate-to-large effect size (Cohen's $d \geq 0.50$) (Cohen, 1988).

Effects of anxiety on ADHD-related impairments

According to these criteria, the following cognitive, EEG and SC variables could be retained for inclusion in the regression models: digit span forward (DSF) and backward (DSB); mean reaction time (MRT), reaction time variability (RTV), the tonic measure of SC level (SCL), and P3 from the baseline condition of the Fast Task; omission errors (OE), commission errors (CE), MRT, RTV, CNV and NoGo-P3 from the CPT-OX; RTV in the congruent and incongruent condition, number of errors in congruent trials (CongE) and in incongruent trials (IncongE), and ERN from the Arrow Flanker task. Since all measures of MRT and RTV across tasks showed large correlations with one another ($r = 0.45-0.76$), only RTV and MRT from the baseline condition of the Fast Task was included, as these variables showed the strongest associations with ADHD (MRT-baseline $d = 0.77$; RTV-baseline $d = 1.23$). Similarly, as DSB and DSF showed a correlation of $r = 0.51$, only DSB was included as this measure showed the highest effect size in ADHD-control differences ($d = 0.70$).

Modelling effects of anxiety

To test the modulating effects of anxiety symptoms on the cognitive, ERP and SC measures, we evaluated the relationship between anxiety symptoms and each measure in the ADHD and control groups, using a series of regression model analyses. Specifically, we modelled each measure as a function of the participant's anxiety symptoms score, diagnostic group, and their interaction (while controlling for the clustering due to sibling relatedness). When a significant interaction between anxiety and group emerged for a measure (i.e., indicating a potentially modulating effect of anxiety on case-control differences), we compared this model with a simpler model testing only the group effect (thus not taking anxiety into account) with likelihood-ratio Chi-square tests. A better fit of the former model would indicate that group differences in the measure may be attenuated with increasing levels of anxiety. To correct for multiple testing, we estimated the equivalent number of effective variables using the correlation matrix of the examined measures (<http://gump.qimr.edu.au/general/daleN/matSpD/>), and performed Bonferroni correction on the total effective tests. The effective number of independent variables was 10.4 and the resulting

Effects of anxiety on ADHD-related impairments

multiple-testing adjusted p-value was 0.0048. Any post-hoc analyses of effects surviving multiple-testing correction used the nominal significance level (0.05).

All cognitive-ERP measures and SCL were log-transformed to normal and standardized prior to analysis, except OE, CE and CongE that were highly skewed and could not be normalized using any transformation method; they were therefore modeled as ordinal. Anxiety scores were also standardized so that beta coefficients represent a standardized effect size measure. Specifically, a 1-standard deviation change in the anxiety symptoms score leads to β change in standard deviation in the examined measures in the overall sample, as well as in the ADHD affected status compared to the unaffected status.

As obsessive-compulsive disorder was classified as an anxiety disorder in previous classification systems (American Psychiatric Association, 2000), regression model analyses were repeated by replacing the anxiety symptom scores with a combined anxiety and obsessive-compulsive trait score.

Since IQ was significantly decreased in the ADHD group in this sample (Cheung et al. 2016, Michelini et al. 2018), we re-ran all analyses covarying for IQ to examine its potential effects on the observed associations. Groups were matched on sex (Table 1) and primary analyses were performed on the whole sample without accounting for sex differences. As the majority of our sample consisted of male participants (80%), a secondary analysis was performed with the female participants (15 ADHD probands and 40 control participants) removed.

RESULTS

Anxiety symptoms in participants with ADHD vs. controls

Individuals with ADHD (mean = 1.6; SD = 2.4; range=0–12) showed significantly higher anxiety symptoms relative to controls (mean = 0.9; SD = 1.6; range = 0–8; $F_{(2,172)} = 5.53$; $p < 0.05$; $d = 0.36$;

Figure 1; Supplementary Figure 1).

Effects of anxiety on ADHD-related impairments

Do anxiety symptoms associate with the cognitive, ERP and skin conductance measures?

The main effect of anxiety symptoms was not significant for any of the examined cognitive, ERP, or electrodermal activity measures (Table 2). For CE on the CPT-OX, but not for any other variable, a significant interaction emerged between anxiety symptoms and group (Table 2). Post-hoc examination of the separate effects of anxiety for each group revealed that higher anxiety symptoms were associated with fewer CE (i.e., with better cognitive performance) in controls ($\beta = -0.37$; 95% CI = -0.65,-0.10; $p < 0.01$), but were not significantly associated with CE in individuals with ADHD (with a positive non-significant coefficient value of $\beta = 0.25$; 95% CI = -0.05,0.57; $p = 0.10$). Together with the negative coefficient for the anxiety x group interaction effect, these results indicate that with increasing anxiety, CE decreased in the control group but not in the ADHD group (Figure 2). Controlling for IQ, the group x anxiety interaction effect for CE on the CPT-OX remained significant, with a negative association of anxiety with CE in the controls but not in individuals with ADHD (Supplementary Table S1). When analyses were repeated including obsessive-compulsive traits to the anxiety scores, no significant effects of anxiety emerged for the examined measures, and the interaction between combined anxiety symptoms scores and group for CE on the CPT-OX reduced in magnitude and became non-significant (Supplementary Table S2).

Do anxiety symptoms modulate the case-control differences on the cognitive, ERP and skin conductance measures?

Follow-up examination of the group effects in the regression model testing the effects of anxiety on CE revealed that, taking into account the effect of anxiety, the group effect on CE was significant ($\beta = 0.41$; 95% CI = 0.02,0.81; $p = 0.04$). This effect size was reduced compared to that observed in a model repeated without taking into account anxiety effects ($\beta = 0.71$; 95% CI = 0.36,1.05; $p < 0.001$; as also reported in Cheung *et al.*, 2016; Michelini *et al.*, 2016). The Chi-square test indicated that the group differences alone accounted for 4.3% of the variation in CE ($\chi^2_{(2,255)} = 16.07$, $p < 0.001$); adding the

Effects of anxiety on ADHD-related impairments

effects of anxiety significantly improved the prediction of CE beyond ADHD-control differences ($R^2 = 0.063$, $\chi^2_{(4,255)} = 24.74$, $p < 0.001$; difference in $R^2 = 0.02$, $\chi^2_{(4,255)} = 9.99$, $p = 0.007$). As a significant interaction only emerged between anxiety symptoms and CE, Chi-square tests were not performed on any of the remaining measures.

Do anxiety symptoms associate with the cognitive, ERP and skin conductance measures in a male-only subsample?

When repeating the analysis with female participants removed, the difference between participants with ADHD and controls on anxiety symptoms remained significant ($d = 0.43$; $F_{(1,159)} = 7.33$, $p < 0.01$). Similarly, results for CE on the CPT-OX remained substantially unchanged in the male-only sample (Table 3): while the interaction between anxiety symptoms and group on CE did not survive multiple-testing correction, the effect size of this interaction effect in the male-only sample ($\beta = 0.59$; Table 3) was similar compared with that of the full sample ($\beta = 0.57$; Table 2). In the male-only sample, additional main effects of anxiety on MRT and RTV on the Fast Task did not survive correction for multiple testing and results remained unchanged for other cognitive-performance measures, the SCL in the Fast Task and all ERP measures (Table 3).

DISCUSSION

We performed a detailed investigation of the modulation effects of anxiety on electrophysiological and electrodermal activity measures, as well as on cognitive performance, in a well-characterised sample of adolescents and young adults with ADHD, and age- and gender-matched controls. We first confirmed previous evidence of increased anxiety symptoms in individuals with ADHD (Elia et al., 2008). Second, analyses revealed that higher anxiety symptoms were associated with better response inhibition in controls, but not in individuals with ADHD, suggesting that individuals with ADHD may not benefit from the hypothesised protective effects of anxiety on inhibitory impairments (Schatz & Rostain, 2006; Tannock, 2009). No effects of anxiety were observed on the remaining cognitive,

Effects of anxiety on ADHD-related impairments

electrophysiological and electrodermal activity measures in the full sample, or on any measure when limiting analyses to a male-only sample.

Using a self-report measure of anxiety symptoms obtained from a validated clinical interview, we found that adolescents and young adults with ADHD in our sample presented with modest to moderate increases in anxiety symptoms relative to neurotypical individuals. This is in line with a large body of evidence showing high rates of comorbid anxiety disorders in individuals with ADHD across the lifespan (Elia et al., 2008; Larson et al., 2011; Solberg et al., 2018). Family and molecular genetic studies also indicate that anxiety disorders are associated with ADHD at the genetic level (Anttila et al., 2017; T. J. Chen et al., 2016; Du Rietz et al., 2018; Michelini, Eley, Gregory, & McAdams, 2015; Schmitz & Mrazek, 2001; Spatola et al., 2007). For the clinician, these findings confirm the importance of implementing early screening of psychiatric symptoms such as anxiety in individuals with ADHD, to ensure efficient intervention strategies as recommended in current UK clinical guidelines (<https://www.nice.org.uk/guidance/qs53>).

Our findings indicate an enhancing role of anxiety on response inhibition in controls and not in individuals with ADHD, as indicated by the significant interaction between anxiety symptoms and ADHD diagnosis on commission errors in the CPT-OX in the full sample. Additionally, we found no significant mitigation effects of anxiety on the remaining cognitive, electrophysiological and electrodermal activity measures, and the mitigation effects of anxiety on inhibition impairments were weaker when obsessive-compulsive traits were included in the anxiety scores. Our results are in line with a recent meta-analysis showing that, when pooling 11 studies which compared youth with ADHD and those with comorbid ADHD-anxiety, there were no differences in attention and working memory impairments in individuals with both ADHD and an anxiety disorder compared to those with ADHD only (Maric et al., 2018). However, our results did not align with previous evidence showing that high anxiety symptoms or anxiety disorders may ameliorate inhibition impairments in individuals with

Effects of anxiety on ADHD-related impairments

ADHD (Bloemsma et al., 2013; Maric et al., 2018; Ruf et al., 2017). It is worth noting that the association between anxiety disorders and reduced impairments in cognitive inhibition was limited to studies with medication-naïve participants in the meta-analysis by Maric and colleagues (2018). The authors suggested that individuals who require pharmacological treatment may show more severe impairments in cognitive functioning (Maric et al., 2018) that are not modifiable with increasing levels of anxiety. Our ADHD sample included all individuals with a combined ADHD presentation at baseline, thus possibly most severe, and with persistent ADHD symptoms and impairments since childhood or adolescence (Cheung et al., 2015), therefore indicating that ADHD-related impairments may not be malleable to the mitigating effects of anxiety at such severe and persistent levels of ADHD symptoms and impairments.

For response inhibition, ADHD-control differences were significantly reduced (from a medium to a small effect size) when controlling for anxiety symptoms. Anxiety symptoms have been hypothesised to enhance effort and increase use of processing resources (Eysenck et al., 2007). Our findings indicate that this hypothesis may hold for controls, but not for individuals with ADHD.

When limiting analyses to male participants, no significant additional effects of anxiety emerged. Unlike the meta-analysis by Maric and colleagues (Maric et al., 2018), we did not find that the presence of anxiety links with attenuated working memory deficits in male participants with ADHD. The lack of beneficial effects of anxiety traits on working memory impairments in our sample may result from the use of the digit span of the Wechsler scale, which yielded heterogeneous results in the previous studies summarised in the recent meta-analysis (Maric et al., 2018). Further studies, using more detailed measures of working memory, i.e., from computerised tasks such as the Cambridge Neuropsychological Test Automated Battery (CANTAB; Morris, Evendon, Sahakian, & Robbins, 1987), will need to clarify this issue further. Suggestive, yet non-significant, associations of anxiety symptoms with faster and less variable RTs in both ADHD and control male-only groups in the present study also

Effects of anxiety on ADHD-related impairments

encourage further investigations of potential sex differences in how anxiety affects cognitive-performance measures.

Certain limitations must be taken into consideration. First, as the group of participants with diagnosed ADHD in our study included a small sample of females ($n = 15$), we could not directly investigate whether there are differences in the effects of anxiety on the cognitive-neurophysiological measures between male and female individuals with ADHD, but were limited to an examination of a male-only sub-sample. Moreover, the age range was wide in our sample. This prevented us from examining whether the impact of anxiety on cognitive-neurophysiological impairments in ADHD may vary with age, similar to a previous report (Maric et al., 2018), as stratifying the analyses by age would have resulted in small samples and low power to detect interaction effects. However, as we controlled for age in all analyses, it is unlikely that our results are confounded by age effects. Future studies using more restricted age ranges and female-only samples should examine these issues further. Furthermore, there is emerging evidence pointing to an association of state anxiety – a transitory emotional response characterized by feelings of apprehension, nervousness and tension (Spielberger et al., 1979) – and ADHD during test performance in young adulthood (Dan & Raz, 2015). While the study of state anxiety was not the scope of this study, further studies examining the possible association of state anxiety and neuro-cognitive impairments in ADHD are warranted.

In conclusion, despite the observed co-occurrence of ADHD and anxiety symptoms, we obtained no evidence consistent with the proposed role of anxiety in modulating cognitive, brain and arousal processes in individuals with ADHD (Bloemsa et al., 2013; Maric et al., 2018; Ruf et al., 2017; Schatz & Rostain, 2006). An ameliorating effect of anxiety symptoms on response inhibition was observed only in controls. Our investigation using a wide range of cognitive and neurophysiological measures thus suggests an overall poor malleability of these impairments in individuals with ADHD irrespective of their levels of anxiety.

Effects of anxiety on ADHD-related impairments

REFERENCES

- Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Mueller, U. C., Hasselhorn, M., . . . Banaschewski, T. (2008). Action monitoring in boys with attention-deficit/hyperactivity disorder, their nonaffected siblings, and normal control subjects: evidence for an endophenotype. *Biological psychiatry*, 64(7), 615-625. doi:10.1016/j.biopsych.2007.12.016
- American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.). In. Washington, DC: Author.
- Angold, A., Costello, E. J., & Erkanli, A. (1999). Comorbidity. *Journal of child psychology and psychiatry, and allied disciplines*, 40(1), 57-87.
- Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R., Bras, J., Duncan, L., . . . Neale, B. (2017). Analysis of shared heritability in common disorders of the brain. *bioRxiv*. doi:10.1101/048991
- Barkley, R. A., & Murphy, K. (2006). *Attention Deficit Hyperactivity Disorder: A Clinical Workbook (3rd ed.)*: New York: Guildford Press.
- Bloemsma, J. M., Boer, F., Arnold, R., Banaschewski, T., Faraone, S. V., Buitelaar, J. K., . . . Oosterlaan, J. (2013). Comorbid anxiety and neurocognitive dysfunctions in children with ADHD. *European child & adolescent psychiatry*, 22(4), 225-234. doi:10.1007/s00787-012-0339-9
- Boucsein, W. (1992). Electrodermal Activity. In. New York: Plenum Press.
- Bowen, R., Chavira, D. A., Bailey, K., Stein, M. T., & Stein, M. B. (2008). Nature of anxiety comorbid with attention deficit hyperactivity disorder in children from a pediatric primary care setting. *Psychiatry research*, 157(1-3), 201-209. doi:10.1016/j.psychres.2004.12.015
- Chen, T. J., Ji, C. Y., Wang, S. S., Lichtenstein, P., Larsson, H., & Chang, Z. (2016). Genetic and environmental influences on the relationship between ADHD symptoms and internalizing problems: A Chinese twin study. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*, 171(7), 931-937. doi:10.1002/ajmg.b.32411

Effects of anxiety on ADHD-related impairments

- Chen, W., Zhou, K., Sham, P., Franke, B., Kuntsi, J., Campbell, D., . . . Asherson, P. (2008). DSM-IV combined type ADHD shows familial association with sibling trait scores: a sampling strategy for QTL linkage. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*, 147b(8), 1450-1460. doi:10.1002/ajmg.b.30672
- Cheung, C. H. M., McLoughlin, G., Brandeis, D., Banaschewski, T., Asherson, P., & Kuntsi, J. (2017). Neurophysiological Correlates of Attentional Fluctuation in Attention-Deficit/Hyperactivity Disorder. *Brain topography*, 30(3), 320-332. doi:10.1007/s10548-017-0554-2
- Cheung, C. H. M., Rijdsdijk, F., McLoughlin, G., Brandeis, D., Banaschewski, T., Asherson, P., & Kuntsi, J. (2016). Cognitive and neurophysiological markers of ADHD persistence and remission. *The British journal of psychiatry : the journal of mental science*, 208(6), 548-555. doi:10.1192/bjp.bp.114.145185
- Cheung, C. H. M., Rijdsdijk, F., McLoughlin, G., Faraone, S. V., Asherson, P., & Kuntsi, J. (2015). Childhood predictors of adolescent and young adult outcome in ADHD. *Journal of psychiatric research*, 62, 92-100. doi:10.1016/j.jpsychires.2015.01.011
- Cohen, J. (1988). Statistical power analysis for the behavioral sciences 2nd edn. In. Hillsdale, New Jersey: Lawrence Erlbaum Associates.
- Craske, M. G., Waters, A. M., Lindsey Bergman, R., Naliboff, B., Lipp, O. V., Negoro, H., & Ornitz, E. M. (2008). Is aversive learning a marker of risk for anxiety disorders in children? *Behaviour research and therapy*, 46(8), 954-967. doi:10.1016/j.brat.2008.04.011
- Dan, O., & Raz, S. (2015). The relationships among ADHD, self-esteem, and test anxiety in young adults. *Journal of attention disorders*, 19(3), 231-239.
- Doehmert, M., Brandeis, D., Imhof, K., Drechsler, R., & Steinhausen, H. C. (2010). Mapping attention-deficit/hyperactivity disorder from childhood to adolescence--no neurophysiologic evidence for a developmental lag of attention but some for inhibition. *Biological psychiatry*, 67(7), 608-616. doi:10.1016/j.biopsych.2009.07.038

Effects of anxiety on ADHD-related impairments

- Du Rietz, E., Coleman, J., Glanville, K., Choi, S. W., O'Reilly, P. F., & Kuntsi, J. (2018). Association of Polygenic Risk for Attention-Deficit/Hyperactivity Disorder With Co-occurring Traits and Disorders. *Biological psychiatry. Cognitive neuroscience and neuroimaging*, 3(7), 635-643. doi:10.1016/j.bpsc.2017.11.013
- Elia, J., Ambrosini, P., & Berrettini, W. (2008). ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. *Child and Adolescent Psychiatry and Mental Health*, 2(1), 15. doi:10.1186/1753-2000-2-15
- Erath, S. A., Tu, K. M., & El-Sheikh, M. (2012). Socially anxious and peer-victimized preadolescents: "doubly primed" for distress? *Journal of abnormal child psychology*, 40(5), 837-848. doi:10.1007/s10802-011-9600-9
- Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion*, 7(2), 336-353. doi:10.1037/1528-3542.7.2.336
- Figner, B., & Murphy, R. O. (2011). Using skin conductance in judgment and decision making research. *A handbook of process tracing methods for decision research*, 163-184.
- Halmoy, A., Fasmer, O. B., Gillberg, C., & Haavik, J. (2009). Occupational outcome in adult ADHD: impact of symptom profile, comorbid psychiatric problems, and treatment: a cross-sectional study of 414 clinically diagnosed adult ADHD patients. *Journal of attention disorders*, 13(2), 175-187. doi:10.1177/1087054708329777
- Humphreys, M. S., & Revelle, W. (1984). Personality, Motivation, and Performance - a Theory of the Relationship between Individual-Differences and Information-Processing. *Psychological review*, 91(2), 153-184. doi:10.1037//0033-295x.91.2.153
- James, S. N., Cheung, C. H., Rijdsdijk, F., Asherson, P., & Kuntsi, J. (2016). Modifiable Arousal in Attention-Deficit/Hyperactivity Disorder and Its Etiological Association With Fluctuating Reaction Times. *Biological psychiatry. Cognitive neuroscience and neuroimaging*, 1(6), 539-547. doi:10.1016/j.bpsc.2016.06.003

Effects of anxiety on ADHD-related impairments

- James, S. N., Cheung, C. H., Rommel, A. S., McLoughlin, G., Brandeis, D., Banaschewski, T., . . . Kuntsi, J. (2017). Peripheral Hypoarousal but Not Preparation-Vigilance Impairment Endures in ADHD Remission. *Journal of attention disorders*, 1087054717698813. doi:10.1177/1087054717698813
- James, S. N., Rommel, A. S., Cheung, C., McLoughlin, G., Brandeis, D., Banaschewski, T., . . . Kuntsi, J. (2017). Association of preterm birth with ADHD-like cognitive impairments and additional subtle impairments in attention and arousal malleability. *Psychological medicine*, 1-13. doi:10.1017/s0033291717002963
- Jensen, P. S., Hinshaw, S. P., Swanson, J. M., Greenhill, L. L., Conners, C. K., Arnold, L. E., . . . Wigal, T. (2001). Findings from the NIMH Multimodal Treatment Study of ADHD (MTA): implications and applications for primary care providers. *J Dev Behav Pediatr*, 22(1), 60-73.
- Johnstone, S. J., Barry, R. J., & Clarke, A. R. (2013). Ten years on: A follow-up review of ERP research in attention-deficit/hyperactivity disorder. *Clinical Neurophysiology*, 124(4), 644-657. doi:https://doi.org/10.1016/j.clinph.2012.09.006
- Klymkiw, D. F., Milligan, K., Lackner, C., Phillips, M., Schmidt, L. A., & Segalowitz, S. J. (2017). Does Anxiety Enhance or Hinder Attentional and Impulse Control in Youth With ADHD? An ERP Analysis. *Journal of attention disorders*, 1087054717707297. doi:10.1177/1087054717707297
- Kooij, J. J. S., & Francken, M. H. (2007). *Diagnostic Interview for ADHD (DIVA) in adults*. Downloaded via www.divacentre.eu.
- Kuntsi, J., Andreou, P., Ma, J., Borger, N. A., & van der Meere, J. J. (2005). Testing assumptions for endophenotype studies in ADHD: reliability and validity of tasks in a general population sample. *BMC Psychiatry*, 5, 40. doi:10.1186/1471-244X-5-40
- Kuntsi, J., Wood, A. C., Rijdsdijk, F., Johnson, K. A., Andreou, P., Albrecht, B., . . . Asherson, P. (2010). Separation of cognitive impairments in attention-deficit/hyperactivity disorder into 2 familial factors. *Archives of general psychiatry*, 67(11), 1159-1167. doi:10.1001/archgenpsychiatry.2010.139

Effects of anxiety on ADHD-related impairments

- Larson, K., Russ, S. A., Kahn, R. S., & Halfon, N. (2011). Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. *Pediatrics*, 127(3), 462-470. doi:10.1542/peds.2010-0165
- Lewis, G., Pelosi, A. J., Araya, R., & Dunn, G. (1992). Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychological medicine*, 22(2), 465-486.
- Lim, C. L., Rennie, C., Barry, R. J., Bahramali, H., Lazzaro, I., Manor, B., & Gordon, E. (1997). Decomposing skin conductance into tonic and phasic components. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*, 25(2), 97-109.
- Maric, M., Bexkens, A., & Bogels, S. M. (2018). Is Clinical Anxiety a Risk or a Protective Factor for Executive Functioning in Youth with ADHD? A Meta-regression Analysis. *Clinical child and family psychology review*. doi:10.1007/s10567-018-0255-8
- McLoughlin, G., Albrecht, B., Banaschewski, T., Rothenberger, A., Brandeis, D., Asherson, P., & Kuntsi, J. (2009). Performance monitoring is altered in adult ADHD: a familial event-related potential investigation. *Neuropsychologia*, 47(14), 3134-3142. doi:10.1016/j.neuropsychologia.2009.07.013
- Michellini, G., Cheung, C. H. M., Kitsune, V., Brandeis, D., Banaschewski, T., McLoughlin, G., . . . Kuntsi, J. (2018). The Etiological Structure of Cognitive-Neurophysiological Impairments in ADHD in Adolescence and Young Adulthood. *Journal of attention disorders*, 1087054718771191. doi:10.1177/1087054718771191
- Michellini, G., Eley, T. C., Gregory, A. M., & McAdams, T. A. (2015). Aetiological overlap between anxiety and attention deficit hyperactivity symptom dimensions in adolescence. *Journal of child psychology and psychiatry, and allied disciplines*, 56(4), 423-431. doi:10.1111/jcpp.12318
- Michellini, G., Kitsune, G. L., Cheung, C. H. M., Brandeis, D., Banaschewski, T., Asherson, P., . . . Kuntsi, J. (2016). Attention-Deficit/Hyperactivity Disorder Remission Is Linked to Better

Effects of anxiety on ADHD-related impairments

- Neurophysiological Error Detection and Attention-Vigilance Processes. *Biological psychiatry*, 80(12), 923-932. doi:http://dx.doi.org/10.1016/j.biopsych.2016.06.021
- Morris, R. C., Evendon, J. L., Sahakian, B. J., & Robbins, T. W. (1987). Computer-aided assessment of dementia: comparative studies of neuropsychological deficits in Alzheimer-type dementia and Parkinson's disease. In *Cognitive Neurochemistry* (ed. S. M. Stahl, S. D. Iverson and E. C. Goodman), pp. 21–36. Oxford: Oxford University Press.
- Moshe, K., Karni, A., & Tirosh, E. (2012). Anxiety and methylphenidate in attention deficit hyperactivity disorder: a double-blind placebo-drug trial. *Attention deficit and hyperactivity disorders*, 4(3), 153-158. doi:10.1007/s12402-012-0078-2
- Newcorn, J. H., Miller, S. R., Ivanova, I., Schulz, K. P., Kalmar, J., Marks, D. J., & Halperin, J. M. (2004). Adolescent outcome of ADHD: impact of childhood conduct and anxiety disorders. *CNS Spectr*, 9(9), 668-678.
- Ruf, B. M., Bessette, K. L., Pearlson, G. D., & Stevens, M. C. (2017). Effect of trait anxiety on cognitive test performance in adolescents with and without attention-deficit/hyperactivity disorder. *Journal of clinical and experimental neuropsychology*, 39(5), 434-448. doi:10.1080/13803395.2016.1232373
- Schatz, D. B., & Rostain, A. L. (2006). ADHD with comorbid anxiety: a review of the current literature. *Journal of attention disorders*, 10(2), 141-149. doi:10.1177/1087054706286698
- Schmitz, S., & Mrazek, D. A. (2001). Genetic and environmental influences on the associations between attention problems and other problem behaviors. *Twin research : the official journal of the International Society for Twin Studies*, 4(6), 453-458.
- Solberg, B. S., Halmoy, A., Engeland, A., Igland, J., Haavik, J., & Klungsoyr, K. (2018). Gender differences in psychiatric comorbidity: a population-based study of 40 000 adults with attention deficit hyperactivity disorder. *Acta psychiatrica Scandinavica*, 137(3), 176-186. doi:10.1111/acps.12845

Effects of anxiety on ADHD-related impairments

- Spatola, C. A., Fagnani, C., Pesenti-Gritti, P., Ogliari, A., Stazi, M. A., & Battaglia, M. (2007). A general population twin study of the CBCL/6-18 DSM-oriented scales. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(5), 619-627. doi:10.1097/CHI.0b013e3180335b12
- Spielberger, C. D., Jacobs, G., Crane, R., Russell, S., Westberry, L., Barker, L., . . . Marks, E. (1979). Preliminary manual for the state-trait personality inventory (STPI). *Unpublished manuscript, University of South Florida, Tampa.*
- Tannock, R. (2009). *ADHD with anxiety disorders*. In T.E. Brown (Ed.), *ADHD comorbidities: Handbook for ADHD complications in children and adults (pp. 131-155)*. Arlington, VA: American Psychiatric Publishing.
- Tye, C., McLoughlin, G., Kuntsi, J., & Asherson, P. (2011). Electrophysiological markers of genetic risk for attention deficit hyperactivity disorder. *Expert reviews in molecular medicine*, 13, e9. doi:10.1017/S1462399411001797
- Wechsler, D. (1991). Wechsler Intelligence Scale for Children (3rd edn). *The Psychological Corporation: London.*
- Wechsler, D. (1997). Wechsler Adult Intelligence Scale (3rd edn.). *The Psychological Corporation: London.*
- Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence (WASI)*. San Antonio, TX: Harcourt Assessment.
- Williams, L. M., Brammer, M. J., Skerrett, D., Lagopoulos, J., Rennie, C., Kozek, K., . . . Gordon, E. (2000). The neural correlates of orienting: an integration of fMRI and skin conductance orienting. *Neuroreport*, 11(13), 3011-3015.
- Williams, R. L. (2000). A note on robust variance estimation for cluster-correlated data. *Biometrics*, 56(2), 645-646.

Effects of anxiety on ADHD-related impairments

TABLES

Table 1. Sample characteristics

	ADHD probands		Controls		Group	
	(n = 87)		(n = 169)		Comparisons	
					$\chi^2_{(2)}$	p
Males, n (%)	72 (83%)		129 (76%)		1.41	0.23
	mean (SD)	range	mean (SD)	range	$F_{(2,172)}$	p
Age, years	18.4 (3.0)	12.1 – 25.9	17.7 (2.2)	11.9 – 21.6	1.73	0.09
IQ	97.9 (14.2)	73 – 129	110.0 (12.4)	73 – 134	37.37	<0.001

Group differences on sex were tested via chi-square test; group differences on other measures were tested with regression models. Group differences between ADHD and control participants were reported in previous analyses on this sample (Cheung *et al.*, 2016, 2017; Michelini *et al.*, 2016). SD: standard deviation.

Effects of anxiety on ADHD-related impairments

Table 2. Results of regression model analyses showing the main effect of anxiety symptoms and the interaction between anxiety symptoms and group on the cognitive-neurophysiological measures

	Anxiety symptoms		Group x Anxiety symptoms	
	β (95% CI)	p	β (95% CI)	p
Memory				
DSB	-0.09 [-0.20;0.02]	0.10	0.04 [-0.18;0.26]	0.70
Fast Task				
MRT-baseline	0.00 [-0.12;0.12]	0.96	0.16 [-0.08;0.40]	0.19
RTV-baseline	-0.05 [-0.19;0.09]	0.46	0.19 [-0.07;0.46]	0.15
SCL-baseline	-0.08 [-0.20;0.04]	0.18	0.01 [-0.23;0.25]	0.92
CPT-OX				
OE	0.05 [-0.18;0.28]	0.70	0.04 [-0.32;0.41]	0.81
CE	-0.16 [-0.39;0.06]	0.16	0.57 [0.21;0.92]	0.002
CNV	-0.01 [-0.10;0.09]	0.88	0.02 [-0.18;0.21]	0.86
NoGo-P3	<0.01 [-0.12;0.11]	0.96	0.14 [-0.09;0.37]	0.23
Arrow Flanker Task				
CongE	0.47 [-0.41;1.35]	0.30	0.15 [-0.15;0.44]	0.34
IncongE	0.06 [-0.05;0.16]	0.27	0.17 [-0.06;0.40]	0.14
ERN	-0.04 [-0.18;0.09]	0.54	-0.19 [-0.45;0.06]	0.14

Results from the final regression model examining associations of anxiety symptoms with the cognitive-neurophysiological measures, as well as the group and the anxiety x group interaction effects, controlling for age. ADHD, attention-deficit/hyperactivity disorder; CI: confidence intervals; CongE, errors in the congruent condition of the arrow Flanker task; CNV, contingent negative variation from the cued-continuous performance test measured at Cz; CPT-OX, cued-continuous performance test; DSB, digit span backward; ERN, error-related negativity amplitude from the arrow Flanker task measured at FCz; IncongE, errors in the incongruent condition of the arrow Flanker task; MRT-baseline, mean reaction time from the baseline condition of the Fast Task; NoGo-P3, P3 amplitude in the NoGo condition from the cued-continuous performance test measured at Cz; OE, omission errors from the cued-continuous performance test; CE, commission errors from the cued-continuous performance test; RTV-baseline, reaction time variability from the baseline condition of the Fast task; SCL-baseline, skin conductance level in the baseline condition of the Fast Task. Boldface indicates P value remains significant following multiple testing (effective number-adjusted P value threshold of 0.0048).

Effects of anxiety on ADHD-related impairments

Table 3. Results of regression model analyses showing the main effect of anxiety symptoms and the interaction between anxiety symptoms and group on the cognitive-neurophysiological measures in the male-only sample

	Anxiety symptoms		Group x Anxiety symptoms	
	β (95% CI)	p	β (95% CI)	p
Memory				
DSB	0.01 [-0.15;0.16]	0.95	0.01 [-0.25;0.28]	0.92
Fast Task				
MRT-baseline	-0.14 [-0.27;-0.01]	0.04	0.24 [-0.01;0.49]	0.06
RTV-baseline	-0.19 [-0.35;-0.04]	0.02	0.28 [-0.01;0.58]	0.06
SCL-baseline	-0.07 [-0.21;0.08]	0.37	0.08 [-0.19;0.36]	0.56
CPT-OX				
OE	0.06 [-0.24;0.37]	0.68	-0.21 [-0.67;0.25]	0.37
CE	-0.11 [-0.42;0.20]	0.49	0.59 [0.10;1.07]	0.02
CNV	-0.05 [-0.19;0.08]	0.44	0.08 [-0.19;0.34]	0.57
NoGo-P3	0.08 [-0.07;0.23]	0.31	0.05 [-0.26;0.37]	0.74
Arrow Flanker Task				
CongE	0.13 [-1.20;1.5]	0.85	0.42 [-0.02;0.85]	0.06
IncongE	0.10 [-0.04;0.24]	0.16	0.28 [-0.01;0.57]	0.06
ERN	0.01 [-0.15;0.17]	0.91	-0.33 [-0.65;-0.01]	0.05

Results from the final regression model examining associations of anxiety symptoms with the cognitive-neurophysiological measures, as well as the group and the anxiety x group interaction effects, controlling for age in males only. ADHD, attention-deficit/hyperactivity disorder; CI: confidence intervals; CongE, errors in the congruent condition of the arrow Flanker task; CNV, contingent negative variation from the cued-continuous performance test measured at Cz; CPT-OX, cued-continuous performance test; DSB, digit span backward; ERN, error-related negativity amplitude from the arrow Flanker task measured at FCz; IncongE, errors in the incongruent condition of the arrow Flanker task; MRT-baseline, mean reaction time from the baseline condition of the Fast task; NoGo-P3, P3 amplitude in the NoGo condition from the cued-continuous performance test measured at Cz; OE, omission errors from the cued-continuous performance test; CE, commission errors from the cued-continuous performance test; RTV-baseline, reaction time variability from the baseline condition of the Fast task; SCL-baseline, skin conductance level in the baseline condition of the Fast Task.

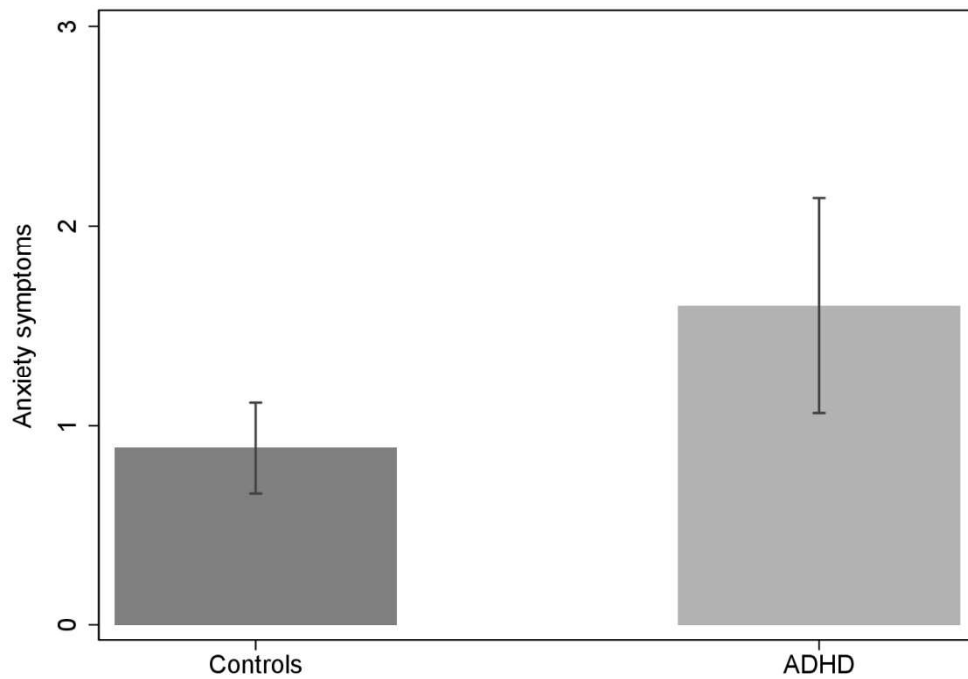


Figure 1. Predicted mean anxiety symptoms in individuals with attention-deficit/hyperactivity disorder (ADHD) and controls. The means are based on estimated anxiety symptoms for each group corrected for age. The error bars represent standard errors.

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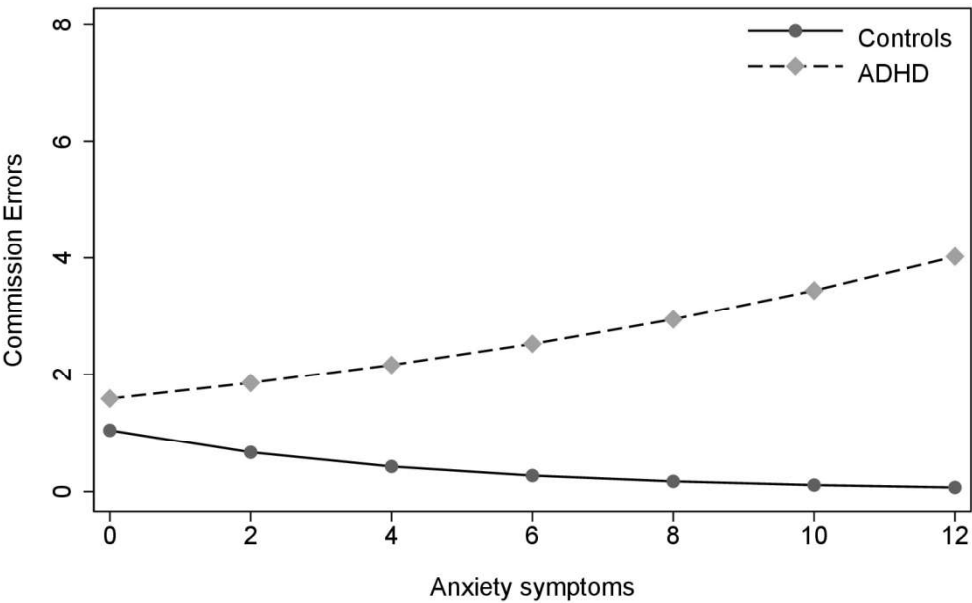


Figure 2. Predicted mean commission errors on the cued-continuous performance test as a function of anxiety symptoms in individuals with attention-deficit/hyperactivity disorder (ADHD) and controls. The means are based on estimated commission errors for each group at each level of anxiety symptoms corrected for age.

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Supplementary material 1: Task details, event related potential (ERP) and skin conductance (SC) extraction.

The Cued-Continuous Performance test (CPT-OX)

For the CPT-OX task, stimuli are presented for 150 ms with a stimulus onset asynchrony of 1.65 s in a pseudorandomized order at the center of a computer monitor. Trials are presented in one block. Task duration is approximately 11 min. Stimulus-locked epochs (stimulus window from -200 to 1650ms) were averaged based on three different response conditions: Cue, Go and NoGo. Averages were calculated for trials with correct responses (Go) or correctly rejected trials (NoGo and Cue), which included at least 20 artefact-free segments. Based on previous research (Albrecht et al., 2013; Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013; McLoughlin et al., 2010), ERP measures were identified within selected electrodes and latency windows for which effects were expected to be largest. These measures were then confirmed separately for each group using topographic maps (Cheung et al., 2017). In Cue trials, the P3 was measured at Pz between 300-650ms, and the CNV was measured at Cz between 1300-1650ms. In Go trials, the P3 was measured at CPz and Pz between 250-500ms. No clear N2 was observed in Go trials, consistent with other studies employing tasks with low conflict-monitoring demands (Gajewski & Falkenstein, 2013; Michelini et al., 2016) and was, therefore, not included in the analysis. In NoGo trials, the P3 was measured at FCz and Cz between 250-550ms and the N2 was measured at Fz between 175-325ms. The CNV was analysed as mean amplitudes between 1300 and 1650ms following cues over the central electrode (Cz). The cue-P3 had a parietal maximum and was defined as the most positive peak between 250 and 600 ms following cue trials at electrode Pz. The nogo-P3 was defined as the most positive peak between 250 and 600 ms following No-Go trials at electrode Cz.

The arrow Flanker task

In the arrow Flanker task, when the target appears, both target and flankers remain on the screen for a further 150 ms, with a new trial being presented every 1.65 s. Trials were arranged in 10 blocks of 40 trials. Task duration is approximately 13 min. Analyses of ERPs of performance monitoring from this task were restricted to the incongruent condition, as the task used in this study is known to elicit strong N2, error related negativity (ERN) and positivity (Pe) components in high-conflict, but not in low-conflict, conditions (Albrecht et al., 2008; McLoughlin et al., 2009). Baseline correction was applied using the -300 to -100 ms pre-target (-200 to 0 ms pre-flanker) interval, following the protocol of previous ERP analyses on the arrow flanker task (Michelini et al., 2016). Data were segmented based on (1) stimulus-locked incongruent trials where a correct response was made and (2) response-locked (error-related) incongruent trials where an incorrect response was made. Individual averages were created based on each condition, requiring ≥ 20 clean segments for each participant. After averaging, the electrodes and latency windows for ERP analyses were selected based on previous studies (Albrecht et al., 2008; Groom et al., 2010; McLoughlin et al., 2009; Michelini et al., 2016) topographic maps and the grand averages. The N2 was measured as maximum negative peak at Fz and FCz between 250-450 ms after target onset. The ERN was defined with respect to the preceding positivity (PNe, -100-50 ms) in order to obtain a more robust measure of this component (23-25), and was measured at FCz between 0-150 ms. The Pe was measured as maximum positive peak at CPz between 150-450 ms after an erroneous response on incongruent trials.

The Fast Task

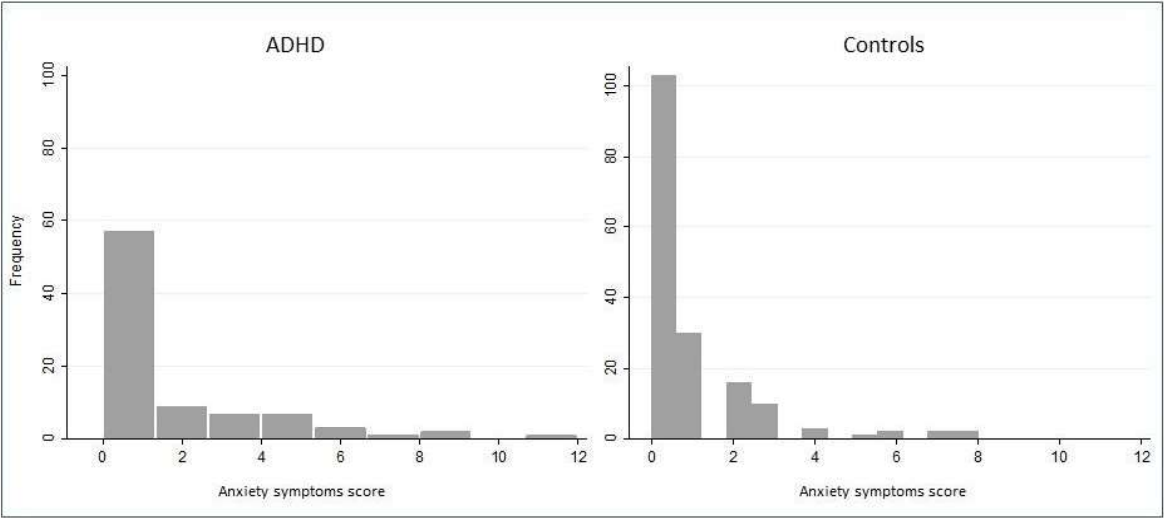
In the Fast Task, stimuli are presented for 8000 ms and for 1000 ms in the baseline and fast-incentive conditions, respectively, after which one of them (the target) was coloured in (Andreou et al., 2007; Kuntsi, Andreou, Ma, Borger, & van der Meere, 2005). Following a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5s

1 followed. P3 amplitude was analysed as the area amplitude measure ($\mu\text{V}\cdot\text{ms}$) at Pz between
2 250 and 450ms, to reduce bias due to the varying noise levels induced by the different task
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7 conditions (Luck, 2005). For the P3 analyses, all the accepted trials were baseline-corrected
8
9 using a pre-stimulus baseline of 200ms. The mean amplitudes of this pre-target period (-
10 200ms - 0ms, using a technical zero baseline as in previous CNV work ^{46,47}) at Cz were also
11
12 analysed separately as a CNV measure. This short interval not only corresponded to the P3
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14 baseline, but also captured the short CNV in the fast-incentive condition with its one-second
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16 cue – target interval (Cheung et al., 2017; James, Cheung, Rijdsdijk, Asherson, & Kuntsi, 2016).
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25 Skin conductance (SC)

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28 SC data values were calculated using a skin conductance system which is based on a SC
29
30 sigmoid-exponential model that allows the tonic measure of SC level (SCL) to be disentangled
31
32 from phasic, stimulus-associated, SC responses (SCR), and further allows the decomposition
33
34 of overlapping SCRs. This system, therefore, is appropriate to use in conditions with long and
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36 short inter-stimulus-intervals. The statistical model was applied to each condition, as a whole.
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38
39
40 SCR amplitude (change in SC from the baseline to the highest point of the SCR) was derived
41
42 from this method, and was calculated on a trial-by-trial basis. The criteria for the smallest SCR
43
44 were set at 0.02 μS . Means of SC variables (SCL) were calculated per participant, across each
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47 condition (James et al., 2016).
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Supplementary Figure 1: Distribution of anxiety symptoms in individuals with attention-deficit/hyperactivity disorder (ADHD) and controls.



Supplementary Table S1. Results of regression model analyses showing main effects of group, anxiety and the interaction between anxiety and group on the cognitive-neurophysiological measures controlling for IQ

	Anxiety symptoms		Group x Anxiety symptoms	
	β (95% CI)	P	β (95% CI)	p
Memory				
DSB	-0.08 [-0.18;0.02]	0.14	0.08 [-0.11;0.27]	0.42
Fast Task				
MRT-baseline	-0.02 [-0.14;0.11]	0.80	0.14 [-0.08;0.35]	0.21
RTV-baseline	-0.06 [-0.20;0.08]	0.37	0.17 [-0.07;0.42]	0.17
SCL-baseline	-0.08 [-0.19;0.05]	0.20	0.02 [-0.22;0.26]	0.85
CPT-OX				
OE	0.01 [-0.18;0.20]	0.89	-0.02 [-0.34;0.32]	0.93
CE	-0.18 [-0.40;0.04]	0.11	0.54 [0.19;0.89]	0.003
CNV	-0.01 [-0.10;0.08]	0.80	0.01 [-0.18;0.20]	0.95
NoGo-P3	0.00 [-0.11;0.11]	0.99	0.15 [-0.08;0.38]	0.21
Arrow Flanker Task				
CongE	0.34 [-0.52;1.19]	0.44	0.08 [-0.19;0.36]	0.57
IncongE	0.05 [-0.05;0.16]	0.31	0.16 [-0.07;0.40]	0.18
ERN	-0.04 [-0.18;0.10]	0.61	-0.18 [-0.44;0.08]	0.18

Results from the regression model examining associations of binary ADHD diagnosis (ADHD vs. control) and anxiety symptoms scores with the cognitive-neurophysiological measures, as well as the anxiety x diagnosis interaction effects, controlling for IQ. ADHD, attention-deficit/hyperactivity disorder; CI: confidence intervals; CongE, errors in the congruent condition of the arrow flanker task; CNV, contingent negative variation from the cued-continuous performance test measured at Cz; CPT-OX, cued-continuous performance test; DSB, digit span backward; ERN, error-related negativity amplitude from the arrow flanker task measured at FCz; IncongE, errors in the incongruent condition of the arrow flanker task; MRT-baseline, mean reaction time from the baseline condition of the Fast task; NoGo-P3, P3 amplitude in the NoGo condition from the cued-continuous performance test measured at Cz; OE, omission errors from the cued-continuous performance test; CE, commission errors from the cued-continuous performance test; RTV-baseline, reaction time variability from the baseline condition of the Fast task; SCL-baseline = skin conductance level in the baseline condition of the Fast Task; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Boldface indicates P value remains significant following multiple testing (effective number-adjusted P value threshold of 0.0048).

Supplementary Table S2. Results of regression model analyses showing main effects of group, combined anxiety (anxiety + obsessive-compulsive) symptoms, and the interaction between combined anxiety and group on the cognitive-neurophysiological measures

	Anxiety symptoms		Group x Anxiety symptoms	
	β (95% CI)	P	β (95% CI)	p
Memory				
DSB	-0.08 [-0.20;0.49]	0.23	-0.01 [-0.24;0.22]	0.90
Fast Task				
MRT-baseline	0.03 [-0.09;0.16]	0.58	0.13 [-0.10;0.37]	0.26
RTV-baseline	-0.02 [-0.14;0.10]	0.76	0.17 [-0.06;0.41]	0.14
SCL-baseline	-0.12 [-0.25;0.02]	0.09	0.04 [-0.24;0.31]	0.79
CPT-OX				
OE	0.1 [-0.12;0.33]	0.36	-0.08 [-0.40;0.24]	0.62
CE	<0.01 [-0.19;0.19]	0.98	0.33 [0.02;0.64]	0.03
CNV	0.03 [-0.05;0.11]	0.48	-0.04 [-0.23;0.15]	0.67
NoGo-P3	-0.06 [-0.18;0.06]	0.33	0.16 [-0.08;0.41]	0.19
Arrow Flanker Task				
CongE	0.47 [-0.44;1.38]	0.31	0.25 [-0.05;0.54]	0.10
IncongE	0.12 [0.02;0.22]	0.02	0.15 [-0.06;0.36]	0.16
ERN	-0.07 [-0.19;0.06]	0.28	-0.11 [-0.35;0.13]	0.35

Results from the regression model examining associations of binary ADHD diagnosis (ADHD vs. control) and combined anxiety-OCD symptoms scores with the cognitive-neurophysiological measures, as well as the anxiety-OCD x diagnosis interaction effects. ADHD, attention-deficit/hyperactivity disorder; CI: confidence intervals; CongE, errors in the congruent condition of the arrow flanker task; CNV, contingent negative variation from the cued-continuous performance test measured at Cz; CPT-OX, cued-continuous performance test; DSB, digit span backward; ERN, error-related negativity amplitude from the arrow flanker task measured at FCz; IncongE, errors in the incongruent condition of the arrow flanker task; MRT-baseline, mean reaction time from the baseline condition of the Fast task; NoGo-P3, P3 amplitude in the NoGo condition from the cued-continuous performance test measured at Cz; OE, omission errors from the cued-continuous performance test; CE, commission errors from the cued-continuous performance test; RTV-baseline, reaction time variability from the baseline condition of the Fast task; SCL-baseline = skin conductance level in the baseline condition of the Fast Task. No P values remain significant following multiple testing (effective number-adjusted P value threshold of 0.0048).

REFERENCES

- Albrecht, B., Brandeis, D., Uebel, H., Heinrich, H., Mueller, U. C., Hasselhorn, M., . . . Banaschewski, T. (2008). Action monitoring in boys with attention-deficit/hyperactivity disorder, their nonaffected siblings, and normal control subjects: evidence for an endophenotype. *Biological psychiatry*, 64(7), 615-625. doi:10.1016/j.biopsych.2007.12.016
- Albrecht, B., Brandeis, D., Uebel, H., Valko, L., Heinrich, H., Drechsler, R., . . . Banaschewski, T. (2013). Familiality of neural preparation and response control in childhood attention deficit-hyperactivity disorder. *Psychological medicine*, 43(9), 1997-2011. doi:10.1017/s003329171200270x
- Andreou, P., Neale, B. M., Chen, W., Christiansen, H., Gabriels, I., Heise, A., . . . Kuntsi, J. (2007). Reaction time performance in ADHD: improvement under fast-incentive condition and familial effects. *Psychological medicine*, 37(12), 1703-1715. doi:10.1017/S0033291707000815
- Cheung, C. H. M., McLoughlin, G., Brandeis, D., Banaschewski, T., Asherson, P., & Kuntsi, J. (2017). Neurophysiological Correlates of Attentional Fluctuation in Attention-Deficit/Hyperactivity Disorder. *Brain topography*, 30(3), 320-332. doi:10.1007/s10548-017-0554-2
- Doehner, M., Brandeis, D., Schneider, G., Drechsler, R., & Steinhausen, H. C. (2013). A neurophysiological marker of impaired preparation in an 11-year follow-up study of attention-deficit/hyperactivity disorder (ADHD). *Journal of child psychology and psychiatry, and allied disciplines*, 54(3), 260-270. doi:10.1111/j.1469-7610.2012.02572.x
- Gajewski, P. D., & Falkenstein, M. (2013). Effects of task complexity on ERP components in Go/Nogo tasks. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*, 87(3), 273-278. doi:10.1016/j.ijpsycho.2012.08.007
- Groom, M. J., Cahill, J. D., Bates, A. T., Jackson, G. M., Calton, T. G., Liddle, P. F., & Hollis, C. (2010). Electrophysiological indices of abnormal error-processing in adolescents with attention deficit hyperactivity disorder (ADHD). *Journal of child psychology and psychiatry, and allied disciplines*, 51(1), 66-76. doi:10.1111/j.1469-7610.2009.02128.x
- James, S. N., Cheung, C. H., Rijdsdijk, F., Asherson, P., & Kuntsi, J. (2016). Modifiable Arousal in Attention-Deficit/Hyperactivity Disorder and Its Etiological Association With Fluctuating Reaction Times. *Biological psychiatry. Cognitive neuroscience and neuroimaging*, 1(6), 539-547. doi:10.1016/j.bpsc.2016.06.003
- Kuntsi, J., Andreou, P., Ma, J., Borger, N. A., & van der Meere, J. J. (2005). Testing assumptions for endophenotype studies in ADHD: reliability and validity of tasks in a general population sample. *BMC Psychiatry*, 5, 40. doi:10.1186/1471-244X-5-40
- McLoughlin, G., Albrecht, B., Banaschewski, T., Rothenberger, A., Brandeis, D., Asherson, P., & Kuntsi, J. (2009). Performance monitoring is altered in adult ADHD: a familial event-related potential investigation. *Neuropsychologia*, 47(14), 3134-3142. doi:10.1016/j.neuropsychologia.2009.07.013
- McLoughlin, G., Albrecht, B., Banaschewski, T., Rothenberger, A., Brandeis, D., Asherson, P., & Kuntsi, J. (2010). Electrophysiological evidence for abnormal preparatory states and inhibitory processing in adult ADHD. *Behavioral and brain functions : BBF*, 6, 66. doi:10.1186/1744-9081-6-66
- Micheli, G., Kitsune, G. L., Cheung, C. H. M., Brandeis, D., Banaschewski, T., Asherson, P., . . . Kuntsi, J. (2016). Attention-Deficit/Hyperactivity Disorder Remission Is Linked to Better Neurophysiological Error Detection and Attention-Vigilance Processes. *Biological psychiatry*, 80(12), 923-932. doi:http://dx.doi.org/10.1016/j.biopsych.2016.06.021